2nd set

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TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	DEC 21	IPC search and display fields enhanced in CA/CAplus with the IPC reform
NEWS 4	DEC 23	New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/ USPAT2
NEWS 5	JAN 13	IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
NEWS 6	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC
NEWS 7	JAN 17	Pre-1988 INPI data added to MARPAT
NEWS 8	JAN 17	IPC 8 in the WPI family of databases including WPIFV
NEWS 9	JAN 30	Saved answer limit increased
NEWS 10	JAN 31	Monthly current-awareness alert (SDI) frequency added to TULSA
NEWS 11	FEB 21	STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results
NEWS 12	FEB 22	Status of current WO (PCT) information on STN
NEWS 13	FEB 22	The IPC thesaurus added to additional patent databases on STN
NEWS 14	FEB 22	Updates in EPFULL; IPC 8 enhancements added
NEWS 15	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS 16	FEB 28	MEDLINE/LMEDLINE reload improves functionality
NEWS 17	FEB 28	TOXCENTER reloaded with enhancements
NEWS 18	FEB 28	REGISTRY/ZREGISTRY enhanced with more experimental spectral property data
NEWS 19	MAR 01	INSPEC reloaded and enhanced
NEWS 20	MAR 03	Updates in PATDPA; addition of IPC 8 data without attributes
NEWS 21	MAR 08	X.25 communication option no longer available after June 2006
NEWS 22	MAR 22	EMBASE is now updated on a daily basis
NEWS 23	APR 03	New IPC 8 fields and IPC thesaurus added to PATDPAFULL
NEWS 24	APR 03	Bibliographic data updates resume; new IPC 8 fields and IPC thesaurus added in PCTFULL
NEWS 25	APR 04	STN AnaVist $500 visualization usage credit offered

NEWS EXPRESS FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT
http://download.cas.org/express/v8.0-Discover/

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* * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 11:58:20 ON 07 APR 2006

=>
Uploading
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Do you want to switch to the Registry File?
Choice (Y/n):
Switching to the Registry File...
Some commands only work in certain files. For example, the EXPAND command can only be used to look at the index in a file which has an index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of commands which can be used in this file.

=> FILE REGISTRY

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 11:58:31 ON 07 APR 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 5 APR 2006 HIGHEST RN 879397-30-5
DICTIONARY FILE UPDATES: 5 APR 2006 HIGHEST RN 879397-30-5

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

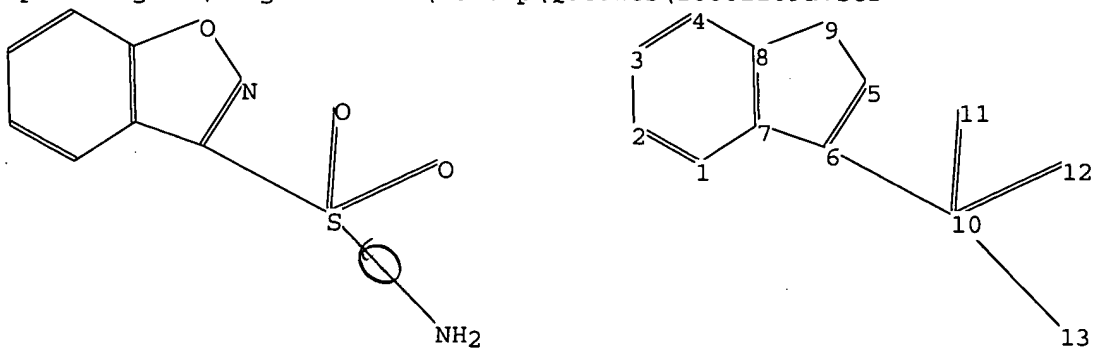
****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=>
Uploading C:\Program Files\Stnexp\Queries\10661109a.str

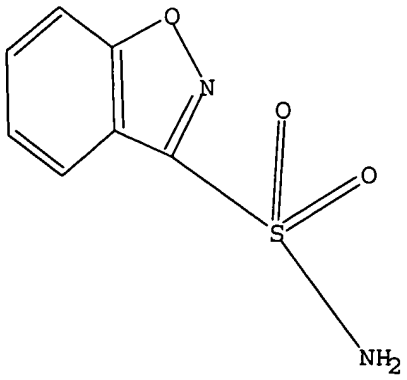


chain nodes :
10 11 12 13
ring nodes :
1 2 3 4 5 6 7 8 9
chain bonds :
6-10 10-11 10-12 10-13
ring bonds :
1-2 1-7 2-3 3-4 4-8 5-6 5-9 6-7 7-8 8-9
exact/norm bonds :
5-6 6-10 10-11 10-12 10-13
exact bonds :
5-9 6-7 8-9
normalized bonds :
1-2 1-7 2-3 3-4 4-8 7-8
isolated ring systems :
containing 1 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:CLASS 11:CLASS 12:CLASS 13:CLASS

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

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=> s l1
SAMPLE SEARCH INITIATED 11:58:47 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        0 TO ITERATE

100.0% PROCESSED         0 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:             0 TO         0
PROJECTED ANSWERS:                0 TO         0

L2             0 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 11:58:53 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -        1 TO ITERATE

100.0% PROCESSED         1 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

L3             0 SEA SSS FUL L1

=>
Uploading C:\Program Files\Stnexp\Queries\10661109b.str
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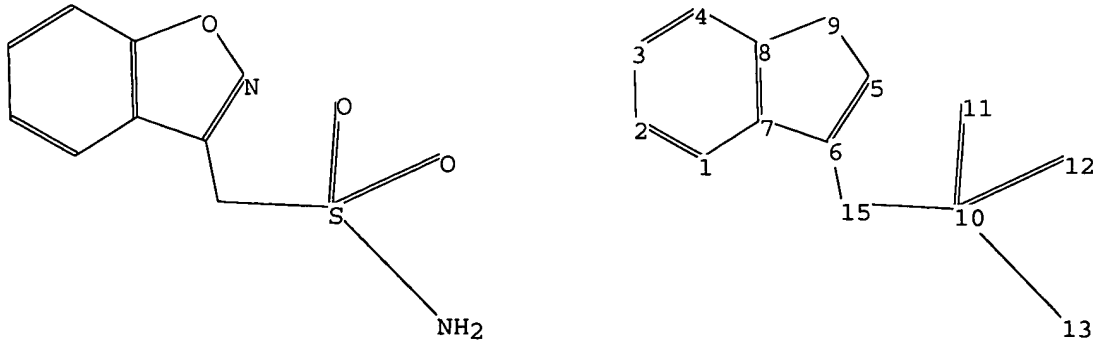
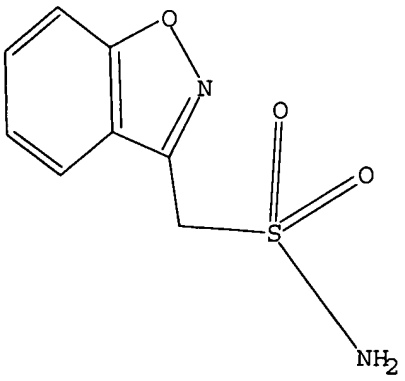


chain nodes :
10 11 12 13 15
ring nodes :
1 2 3 4 5 6 7 8 9
chain bonds :
6-15 10-13 10-11 10-12 10-15
ring bonds :
1-2 1-7 2-3 3-4 4-8 5-6 5-9 6-7 7-8 8-9
exact/norm bonds :
5-6 10-13 10-11 10-12 10-15
exact bonds :
5-9 6-7 6-15 8-9
normalized bonds :
1-2 1-7 2-3 3-4 4-8 7-8
isolated ring systems :
containing 1 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:CLASS
11:CLASS 12:CLASS 13:CLASS 15:CLASS

L4 STRUCTURE UPLOADED

=> d l4
L4 HAS NO ANSWERS
L4 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l4
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SAMPLE SCREEN SEARCH COMPLETED - 6 TO ITERATE

100.0% PROCESSED 6 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 6 TO 266

PROJECTED ANSWERS: 2 TO 124

L5 2 SEA SSS SAM L4

=> s l4 sss full
FULL SEARCH INITIATED 12:01:23 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 100 TO ITERATE

100.0% PROCESSED 100 ITERATIONS 21 ANSWERS
SEARCH TIME: 00.00.01

L6 21 SEA SSS FUL L4

=> FIL HCAPLUS
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	335.20	335.41

FILE 'HCAPLUS' ENTERED AT 12:01:36 ON 07 APR 2006
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 7 Apr 2006 VOL 144 ISS 16
FILE LAST UPDATED: 6 Apr 2006 (20060406/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l6
L7 418 L6

=> s l7 and 4-hydroxy-coumarin
5300847 4
437460 HYDROXY
9 HYDROXIES
437469 HYDROXY
(HYDROXY OR HYDROXIES)
23205 COUMARIN
6887 COUMARINS
24885 COUMARIN
(COUMARIN OR COUMARINS)
98 4-HYDROXY-COUMARIN
(4(W)HYDROXY(W)COUMARIN)
L8 1 L7 AND 4-HYDROXY-COUMARIN

```
=> s l7 and coumarin
         23205 COUMARIN
          6887 COUMARINS
         24885 COUMARIN
                  (COUMARIN OR COUMARINS)
L9             3 L7 AND COUMARIN

=> s l7 and process
       2224636 PROCESS
       1503133 PROCESSES
       3319380 PROCESS
                  (PROCESS OR PROCESSES)
L10           24 L7 AND PROCESS

=> s l10 and coumarin
         23205 COUMARIN
          6887 COUMARINS
         24885 COUMARIN
                  (COUMARIN OR COUMARINS)
L11            2 L10 AND COUMARIN

=> s l10 and hydroxyl amine
        113341 HYDROXYL
          3835 HYDROXYLS
        115579 HYDROXYL
                  (HYDROXYL OR HYDROXYLS)
        265000 AMINE
        247945 AMINES
        404509 AMINE
                  (AMINE OR AMINES)
           346 HYDROXYL AMINE
                  (HYDROXYL(W)AMINE)
L12            0 L10 AND HYDROXYL AMINE

=> s l10 and py<=2001
      21808418 PY<=2001
L13            2 L10 AND PY<=2001

=> d his

     (FILE 'HOME' ENTERED AT 11:58:20 ON 07 APR 2006)

     FILE 'REGISTRY' ENTERED AT 11:58:31 ON 07 APR 2006
L1               STRUCTURE UPLOADED
L2             0 S L1
L3             0 S L1 SSS FULL
L4               STRUCTURE UPLOADED
L5             2 S L4
L6            21 S L4 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 12:01:36 ON 07 APR 2006
L7           418 S L6
L8             1 S L7 AND 4-HYDROXY-COUMARIN
L9             3 S L7 AND COUMARIN
L10           24 S L7 AND PROCESS
L11            2 S L10 AND COUMARIN
L12            0 S L10 AND HYDROXYL AMINE
L13            2 S L10 AND PY<=2001
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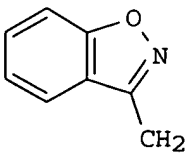
=> d l8 ibib abs hitstr tot

L8 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:695963 HCAPLUS
DOCUMENT NUMBER: 137:216942
TITLE: Process for the preparation of 1,2-benzisoxazole-3-acetic acid, an intermediate in the synthesis of Zonisamide
INVENTOR(S): Mendelovici, Mariorara; Nidam, Tamar
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002070495	A1	20020912	WO 2002-US6419	20020304
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2440030	AA	20020912	CA 2002-2440030	20020304
US 2002183525	A1	20021205	US 2002-90710	20020304
US 6677458	B2	20040113		
EP 1373229	A1	20040102	EP 2002-717527	20020304
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004049053	A1	20040311	US 2003-661109	20030912

PRIORITY APPLN. INFO.:		
US 2001-273172P	P	20010302
US 2001-294847P	P	20010531
US 2002-90710	A3	20020304
WO 2002-US6419	W	20020304

OTHER SOURCE(S): CASREACT 137:216942
GI



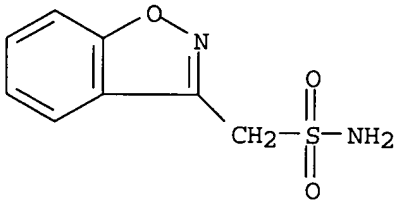
CH_2-CO_2H I

AB A process for the preparation of 1,2-benzisoxazole-3-acetic acid (I) from 4-hydroxycoumarin and hydroxylamine.HCl in the presence of a base is disclosed. Compound I has com. importance as a key intermediate in the preparation of Zonisamide. For example, a solution of 4-hydroxycoumarin (100 g),

hydroxylamine hydrochloride (150 g) and diethylamine (160 g) in MeOH (500 mL) was heated at reflux for 1 h. The reaction mixture was evaporated to dryness and the solid dissolved in aqueous NaHCO3 and extracted with ether. After acidification of the aqueous phase, the product was isolated by filtration, washed with water and dried to provide I (99.82 g) in 93 % weight/weight yield. Avantages of the present invention are: (1) the prepare of I without the use of metallic sodium; and (2) the minimization of reaction side-products, e.g., oxime. The process is thus substantially less hazardous than previous methods. The invention also claims the prepare I or salts of which are converted to 1,2-benzisoxazole-3-methanesulfonamide, i.e., zonisamide.

IT **68291-97-4P**, 1,2-Benzisoxazole-3-methanesulfonamide
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(product; process for preparation of 1,2-benzisoxazole-3-acetic acid, an intermediate in synthesis of zonisamide)

RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d 19 ibib abs hitstr tot

L9 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:517720 HCAPLUS
DOCUMENT NUMBER: 143:128034
TITLE: Comparative evaluation of oral systemic exposure of 56 xenobiotics in rat, dog, monkey and human
AUTHOR(S): Ward, K. W.; Nagilla, R.; Jolivette, L. J.
CORPORATE SOURCE: Preclinical Drug Discovery, Cardiovascular & Urogenital Centre of Excellence in Drug Discovery, GlaxoSmithKline, King of Prussia, PA, USA
SOURCE: Xenobiotica (2005), 35(2), 191-210
CODEN: XENOBH; ISSN: 0049-8254
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

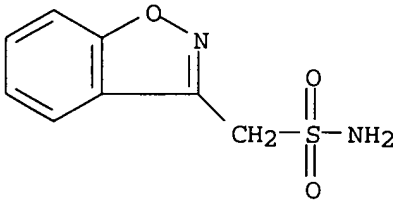
AB The prediction of human pharmacokinetics is often based on in vivo preclin. pharmacokinetic data. However, to date, no clear guidance was available about the relative ability of the major preclin. species to estimate human oral exposure. The study was conducted to survey the literature on oral pharmacokinetic parameters in rat, dog, monkey and human, and to compare various methods for prediction of oral exposure in humans. Fifty-six non-peptide xenobiotics were identified with oral pharmacokinetic data in rat, dog, monkey and human, and comparison of the data from each species to humans was conducted along with an evaluation of the mol. features of these compds. Monkey liver blood flow-based oral

exposure was qual. and quant. more predictive of human oral exposure than rat or dog. Furthermore, generation of data in 3 vs. 2 preclin. species did not always improve human predictivity. The use of mol. properties did not substantially improve the prediction of human oral exposure compared with the prediction from monkey alone. These observations confirm the continued importance of non-human primates in preclin. pharmacokinetics, and also have implications for pharmacokinetic lead optimization and for prediction of human pharmacokinetic parameters from in vivo preclin. data.

IT **68291-97-4**, AD-810
RL: ADV (Adverse effect, including toxicity); PRP (Properties); BIOL (Biological study)
(oral xenobiotics pharmacokinetics and toxic effects in rat, dog, monkey relation to hepatic circulation and mol. structure to predict human oral toxicity)

RN 68291-97-4 HCAPLUS

CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:429406 HCAPLUS

DOCUMENT NUMBER: 142:482033

TITLE: A process for the manufacture of zonisamide, useful as anticonvulsant agent

INVENTOR(S): Jaweed Mukarram, Siddiqui Mohammed; Merwade, Aravind Yehanathsa; Shukla, Jagdish Dattopant; Saiyad, Anis Mushtaqeali

PATENT ASSIGNEE(S): Wockhardt Limited, India

SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

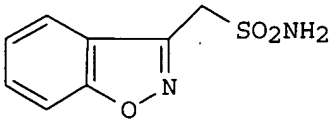
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005044808	A1	20050519	WO 2003-IB5052	20031111

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

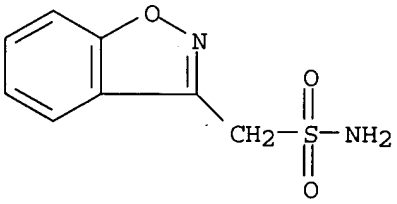
AU 2003276531 A1 20050526 AU 2003-276531 20031111
PRIORITY APPLN. INFO.: WO 2003-IB5052 A 20031111
OTHER SOURCE(S): CASREACT 142:482033
GI



I

AB The invention relates to an improved process for the preparation of zonisamide (I), a well known anticonvulsant. Other aspects of this invention are isolation of a key intermediate, viz., isolation of crystalline sodium chloride associated with 1,2-benzisoxazole-3-methane sodium sulfonate (BOS-Na:NaCl). Zonisamide (I, 99% HPLC purity) was prepared via ring opening/cyclization of 4-hydroxycoumarin in the presence of NH2OH (step 1), sulfonation of the obtained 1,2-benzisoxazole-3-acetic acid, and chlorination/amidation of the obtained sodium 1,2-benzisoxazole-3-methanesulfonate associated with NaCl (yield of step 1 was 95-98%). The anal. characteristics like IR and XRD data of BOS-Na:NaCl were also reported to confirm its nature.

IT **68291-97-4P**, Zonisamide
RL: IMF (Industrial manufacture); PRP (Properties); PREP (Preparation)
(process for the manufacture of zonisamide useful as anticonvulsant agent)
RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

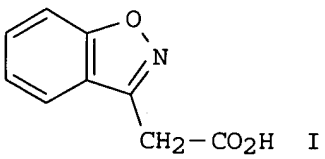
L9 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:695963 HCAPLUS
DOCUMENT NUMBER: 137:216942
TITLE: Process for the preparation of 1,2-benzisoxazole-3-acetic acid, an intermediate in the synthesis of zonisamide
INVENTOR(S): Mendelovici, Mariorara; Nidam, Tamar
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

WO 2002070495	A1	20020912	WO 2002-US6419	20020304
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2440030	AA	20020912	CA 2002-2440030	20020304
US 2002183525	A1	20021205	US 2002-90710	20020304
US 6677458	B2	20040113		
EP 1373229	A1	20040102	EP 2002-717527	20020304
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004049053	A1	20040311	US 2003-661109	20030912
PRIORITY APPLN. INFO.:			US 2001-273172P	P 20010302
			US 2001-294847P	P 20010531
			US 2002-90710	A3 20020304
			WO 2002-US6419	W 20020304

OTHER SOURCE(S): CASREACT 137:216942

GI



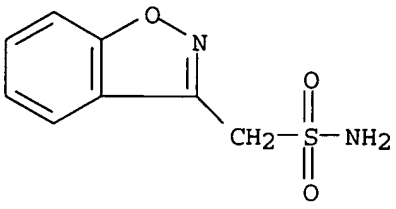
CH_2-CO_2H I

AB A process for the preparation of 1,2-benzisoxazole-3-acetic acid (I) from 4-hydroxycoumarin and hydroxylamine.HCl in the presence of a base is disclosed. Compound I has com. importance as a key intermediate in the preparation of Zonisamide. For example, a solution of 4-hydroxycoumarin (100 g), hydroxylamine hydrochloride (150 g) and diethylamine (160 g) in MeOH (500 mL) was heated at reflux for 1 h. The reaction mixture was evaporated to dryness and the solid dissolved in aqueous NaHCO3 and extracted with ether. After acidification of the aqueous phase, the product was isolated by filtration, washed with water and dried to provide I (99.82 g) in 93 % weight/weight yield. Avantages of the present invention are: (1) the prepare of I without the use of metallic sodium; and (2) the minimization of reaction side-products, e.g., oxime. The process is thus substantially less hazardous than previous methods. The invention also claims the prepare I or salts of which are converted to 1,2-benzisoxazole-3-methanesulfonamide, i.e., zonisamide.

IT **68291-97-4P**, 1,2-Benzisoxazole-3-methanesulfonamide
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(product; process for preparation of 1,2-benzisoxazole-3-acetic acid, an intermediate in synthesis of zonisamide)

RN 68291-97-4 HCAPLUS

CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



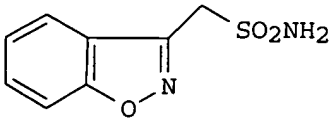
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l11 ibib abs hitstr tot

L11 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:429406 HCAPLUS
DOCUMENT NUMBER: 142:482033
TITLE: A **process** for the manufacture of zonisamide, useful as anticonvulsant agent
INVENTOR(S): Jaweed Mukarram, Siddiqui Mohammed; Merwade, Aravind Yehanathsa; Shukla, Jagdish Dattopant; Saiyad, Anis Mushtaqeali
PATENT ASSIGNEE(S): Wockhardt Limited, India
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005044808	A1	20050519	WO 2003-IB5052	20031111
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003276531	A1	20050526	AU 2003-276531	20031111

PRIORITY APPLN. INFO.: WO 2003-IB5052 A 20031111
OTHER SOURCE(S): CASREACT 142:482033
GI



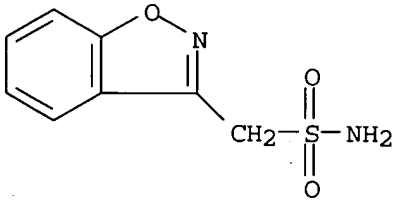
I

AB The invention relates to an improved **process** for the preparation of zonisamide (I), a well known anticonvulsant. Other aspects of this invention are isolation of a key intermediate, viz., isolation of crystalline sodium chloride associated with 1,2-benzisoxazole-3-methane sodium sulfonate (BOS-Na:NaCl). Zonisamide (I, 99% HPLC purity) was prepared via ring opening/cyclization of 4-hydroxycoumarin in the presence of NH2OH (step 1), sulfonation of the obtained 1,2-benzisoxazole-3-acetic acid, and chlorination/amidation of the obtained sodium 1,2-benzisoxazole-3-methanesulfonate associated with NaCl (yield of step 1 was 95-98%). The anal. characteristics like IR and XRD data of BOS-Na:NaCl were also reported to confirm its nature.

IT **68291-97-4P**, Zonisamide
RL: IMF (Industrial manufacture); PRP (Properties); PREP (Preparation)
(**process** for the manufacture of zonisamide useful as anticonvulsant agent)

RN 68291-97-4 HCAPLUS

CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:695963 HCAPLUS
DOCUMENT NUMBER: 137:216942
TITLE: **Process** for the preparation of 1,2-benzisoxazole-3-acetic acid, an intermediate in the synthesis of zonisamide
INVENTOR(S): Mendelovici, Mariorara; Nidam, Tamar
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002070495	A1	20020912	WO 2002-US6419	20020304

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,

CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2440030	AA	20020912	CA 2002-2440030		20020304
US 2002183525	A1	20021205	US 2002-90710		20020304
US 6677458	B2	20040113			
EP 1373229	A1	20040102	EP 2002-717527		20020304
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
US 2004049053	A1	20040311	US 2003-661109		20030912
PRIORITY APPLN. INFO.:			US 2001-273172P	P	20010302
			US 2001-294847P	P	20010531
			US 2002-90710	A3	20020304
			WO 2002-US6419	W	20020304

OTHER SOURCE(S): CASREACT 137:216942
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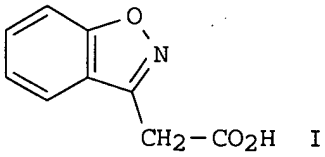
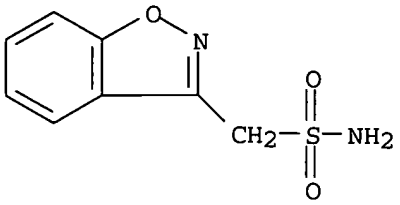


I

AB A **process** for the preparation of 1,2-benzisoxazole-3-acetic acid (I) from 4-hydroxycoumarin and hydroxylamine.HCl in the presence of a base is disclosed. Compound I has com. importance as a key intermediate in the preparation of Zonisamide. For example, a solution of 4-hydroxycoumarin (100 g), hydroxylamine hydrochloride (150 g) and diethylamine (160 g) in MeOH (500 mL) was heated at reflux for 1 h. The reaction mixture was evaporated to dryness and the solid dissolved in aqueous NaHCO3 and extracted with ether. After acidification of the aqueous phase, the product was isolated by filtration, washed with water and dried to provide I (99.82 g) in 93 % weight/weight yield. Avantages of the present invention are: (1) the prepare of I without the use of metallic sodium; and (2) the minimization of reaction side-products, e.g., oxime. The **process** is thus substantially less hazardous than previous methods. The invention also claims the prepare I or salts of which are converted to 1,2-benzisoxazole-3-methanesulfonamide, i.e., zonisamide.

IT **68291-97-4P**, 1,2-Benzisoxazole-3-methanesulfonamide
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(product; **process** for preparation of 1,2-benzisoxazole-3-acetic acid, an intermediate in synthesis of zonisamide)

RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



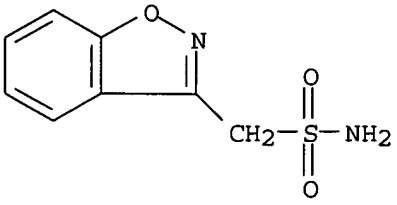
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l13 ibib abs hitstr tot

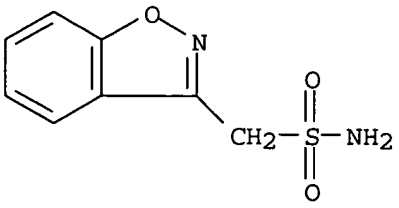
L13 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:75746 HCAPLUS
DOCUMENT NUMBER: 126:180780
TITLE: Pharmacokinetic study of zonisamide in patients undergoing brain surgery
AUTHOR(S): Ieiri, Ichiro; Morioka, Takato; Kim, Sonyori; Nishio, Shunji; Fukui, Masashi; Higuchi, Shun
CORPORATE SOURCE: Division of Pharmaceutical Science, Kyushu University, Fukuoka, Japan
SOURCE: Journal of Pharmacy and Pharmacology (**1996**), 48(12), 1270-1275
CODEN: JPPMAB; ISSN: 0022-3573
PUBLISHER: Royal Pharmaceutical Society of Great Britain
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To test whether the concentration of the anticonvulsant zonisamide in erythrocytes reflects the brain concentration and the clin. response of the drug, its pharmacokinetics were studied in nine patients undergoing surgery for brain tumor. Erythrocyte, total, and free serum concns. in samples drawn on the day of brain surgery were compared with levels on a day after the operation. In three patients zonisamide and its major metabolite, 2-sulfamoylacetylphenol, were also analyzed in urine. The area under the curve of the free and the erythrocyte concentration did not differ between the two study phases whereas the area under the curve of the total serum concentration was significantly lower on the day of the operation, and this was associated with significant increases in total clearance (15.4 compared with 12.7 mL kg-1 h-1, $P < 0.05$, $n = 9$) and renal clearance (5.4 compared with 3.3 mL kg-1 h-1, $P < 0.05$, $n = 3$), and non-significant change in non-renal clearance (7.7 on the day of operation compared with 8.4 mL kg-1 h-1 on the post-operation day, $n = 3$). Zonisamide distribution was also altered by the operative procedure, as evidenced by a higher volume of distribution (1.48 compared with 0.87 L kg-1, $P < 0.05$, $n = 9$). The binding of zonisamide was characterized on both days. Zonisamide binding to erythrocytes seemed to occur by two **processes**: a saturable **process** and a non-saturable linear **process.** The maximum binding capacity to erythrocytes (31.6 vs. 29.7 μg mL-1) did not differ on the two days; however, increases in the dissociation binding constant (+28%) and the proportionality constant (+24%) were observed on the day of the operation, suggesting that the zonisamide concentration in erythrocytes was greater on the day of the operation. Brain surgery appears to be one of the possible factors altering the rate of elimination of zonisamide and the uptake of the drug by erythrocytes.

IT **68291-97-4**, Zonisamide
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(pharmacokinetic study of zonisamide in humans undergoing brain surgery)
RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



L13 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:215 HCAPLUS
DOCUMENT NUMBER: 112:215
TITLE: Binding of sulfonamides to erythrocyte proteins and possible drug-drug interaction
AUTHOR(S): Matsumoto, Katashi; Miyazaki, Hisashi; Fujii, Toshihiko; Amejima, Hideki; Furukawa, Hideo; Hashimoto, Masahisa
CORPORATE SOURCE: Res. Lab., Dainippon Pharm. Co., Ltd., Suita, 564, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (**1989**), 37(10), 2807-10
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mode of binding of sulfonamides to erythrocyte proteins and possible drug-drug interaction between those compds. in erythrocytes resulting in changes in tissue levels were studied in rats using zonisamide (a novel antiepileptic agent possessing a sulfonamide group), several other sulfonamides, and some antiepileptics without a sulfonamide group. In Michaelis-Menten plottings, the sulfonamide was concentrated into erythrocytes in vitro and in vivo in a saturable high-affinity mode and in a linear low-affinity mode at ordinary therapeutic plasma levels through a simple diffusion **process.** Concentration in erythrocytes was affected by the presence of albumin in the extracellular medium. The cellular sulfonamide was readily replaced by extracellular sulfonamide in vitro. Even in vivo, erythrocyte levels of zonisamide were lowered by administration of other sulfonamides, although the plasma and tissue levels were not changed since the plasma and tissue compartments of zonisamide were large relative to the erythrocyte compartment at ordinary therapeutic dose levels of zonisamide in animals and man. Therefore, disposition of zonisamide was not influenced by other sulfonamides, but drug-drug interactions affecting the tissue levels may occur for a combination of sulfonamides with extremely different affinities for erythrocytes and low therapeutic plasma levels.
IT **68291-97-4**, Zonisamide
RL: BIOL (Biological study)
(binding of, by erythrocyte, other sulfonamides effect on)
RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



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L10 ANSWER 1 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:238357 HCAPLUS
TITLE: Preparation, compositions and uses of mixtures of polypeptides
INVENTOR(S): Pinchasi, Irit; Dolitzky, Ben-Zion; Frenkel, Anton; Schwartz, Michal; Arnon, Ruth; Aharoni, Rina
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries, Ltd., Israel; Teva Pharmaceuticals USA, Inc.; Yeda Research and Development Co. Ltd.
SOURCE: PCT Int. Appl., 197 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006029411	A2	20060316	WO 2005-US32553	20050909

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-608844P P 20040909

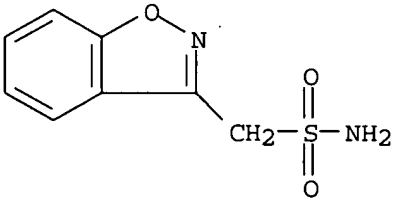
AB The invention provides a composition comprising a mixture of polypeptides, wherein each polypeptide (a) is a copolymer of the amino acids L-glutamic acid, L-alanine, L-tyrosine, and L-lysine, and (b) may be in the form of a pharmaceutically acceptable salt. In the mixture (i) the polypeptides have an average mol. weight in the range 13,500 to 18,500 daltons, (ii) 13% to 38% of the polypeptides have a diethylamide group instead of a carboxyl group present at one end thereof, and (iii) 68% of the polypeptides have a mol. weight between 7000 and 41,000 daltons. The average mol. weight of polypeptides is 16,000 daltons. **Processes** for preparing the mixture of polypeptides and its therapeutic uses are described. For example, an injection

formulation containing the polypeptide mixture 5 mg, mannitol 50 mg, and water for injection to 1.0 mL was prepared and packaged in Hypak syringe. Also, the biol. activity of prepns. of different mol. weight (MW) was evaluated by their ability to block the induction of exptl. autoimmune encephalomyelitis (EAE) in mice by reducing the number of sick animals and lowering the severity of disease (clin. score). The results were compared to that of glatiramer acetate (GA). The effect of increase in MW on biol. activity was observed At the dose of 25 μg/mouse, GA blocking activity was suboptimal while prepns. with MW ranging between 15 and 20 KDa were more effective in inhibiting acute EAE. At the dose of 50 μg/mouse, GA (7.5 daltons) was not effective in inhibiting chronic myelin oligodendrocyte glycoprotein (MOG)-induced EAE, while the mixture of polypeptides of the invention (.apprx. 16.0 KD) had a significant inhibitory effect.

IT **68291-97-4**, Zonisamide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic combinations containing mixts. of polypeptides comprising alanine, glutamic acid, lysine and tyrosine)

RN 68291-97-4 HCAPLUS

CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



L10 ANSWER 2 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:100738 HCAPLUS

DOCUMENT NUMBER: 144:198849

TITLE: Novel dosage form comprising modified-release and immediate-release active ingredients

INVENTOR(S): Vaya, Navin; Karan, Rajesh Singh; Sadanand, Sunil; Gupta, Vinod Kumar

PATENT ASSIGNEE(S): India

SOURCE: U.S. Pat. Appl. Publ., 49 pp., Cont.-in-part of U.S. Ser. No. 630,446.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

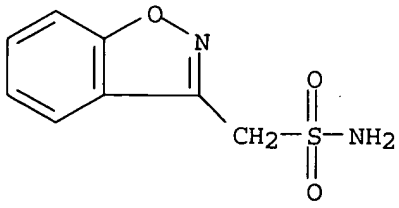
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2006024365	A1	20060202	US 2005-134633		20050519
US 2004096499	A1	20040520	US 2003-630446		20030729
PRIORITY APPLN. INFO.:			IN 2002-MU697	A	20020805
			IN 2002-MU699	A	20020805
			IN 2003-MU80	A	20030122
			IN 2003-MU82	A	20030122
			US 2003-630446	A2	20030729

AB A dosage form comprising of a high dose, high solubility active ingredient as modified release and a low dose active ingredient as immediate release

where the weight ratio of immediate release active ingredient and modified release active ingredient is from 1:10 to 1:15000 and the weight of modified release active ingredient per unit is from 500 mg to 1500 mg; a **process** for preparing the dosage form. Tablets containing 10 mg sodium pravastatin and 1000 mg niacin were prepared The release of sodium pravastatin after 24 h was 67.7%, and the release of niacin after 1 h was 84.1%.

IT **68291-97-4**, Zonisamide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel dosage form comprising modified-release and immediate-release active ingredients)
RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



L10 ANSWER 3 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:33913 HCAPLUS
DOCUMENT NUMBER: 144:128959
TITLE: Two crystalline forms of sodium 1,2-benzisoxazole-3-methanesulfonate, and **processes** for the preparation and use thereof in the synthesis of zonisamide
INVENTOR(S): Naddaka, Vladimir; Adin, Itai; Klopfer, Eyal; Arad, Oded; Kaspi, Joseph
PATENT ASSIGNEE(S): Israel
SOURCE: U.S. Pat. Appl. Publ., 20 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2006009644	A1	20060112	US 2005-153403		20050616
US 2006014814	A1	20060119	US 2005-153402		20050616
PRIORITY APPLN. INFO.:			US 2004-580360P	P	20040618
			US 2004-582086P	P	20040624
			US 2004-622009P	P	20041027

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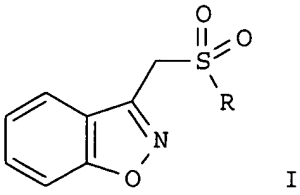


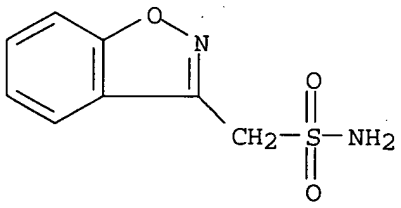
I

AB Disclosed is a **process** of preparing 1,2-benzisoxazole-3-methanesulfonamide (zonisamide). Also disclosed is (1) a method of dehydrating sodium 1,2-benzisoxazole-3-methanesulfonate monohydrate (I.H2O; R = ONa), a compound useful in the preparation of zonisamide (I; R = NH2), as well as (2) the crystalline forms of the dehydrated salt, sodium 1,2-benzisoxazole-3-methanesulfonate (I; R = ONa). The hydrate I.H2O (R = ONa) was prepared by sulfonylation of 3-(bromomethyl)-1,2-benzisoxazole with sodium sulfite. Compound I.H2O (R = ONa) was dehydrated by azeotropic distillation from toluene or toluene/DMF to give two crystalline forms of the dehydrated I, as determined by X-ray powder diffraction. Either form of dehydrated I (R = ONa) reacted with oxalyl chloride to give the corresponding sulfonyl chloride, which was treated in situ with ammonia to give zonisamide.

IT **68291-97-4P**, Zonisamide
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation and crystalline forms of sodium 1,2-benzisoxazole-3-methanesulfonate and use in the synthesis of zonisamide)

RN 68291-97-4 HCAPLUS

CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



L10 ANSWER 4 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1050940 HCAPLUS

DOCUMENT NUMBER: 143:326350

TITLE: One-pot **process** for the preparation of 1,2-benzisoxazole-3-methanesulfonamide from 4-hydroxycoumarin

INVENTOR(S): Ueno, Yoshikazu; Ishikura, Tsutomu

PATENT ASSIGNEE(S): Japan

SOURCE: U.S. Pat. Appl. Publ., 5 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005215796	A1	20050929	US 2005-88802	20050325
WO 2005092869	A1	20051006	WO 2005-JP5349	20050324

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

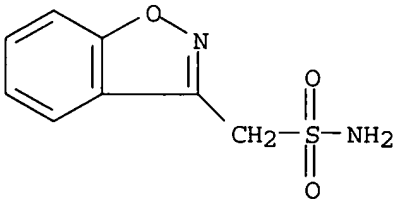
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-556073P P 20040325
OTHER SOURCE(S): CASREACT 143:326350

AB 1,2-Benzisoxazole-3-methanesulfonamide was prepared by reaction of 4-hydroxycoumarin and NH2OH (salt) in H2O to give a mixture, acidification of the mixture and addition of ClCH2CH2Cl, removal of the aqueous layer to give a mixture containing 1,2-benzisoxazole-3-acetic acid and ClCH2CH2Cl, further removal of H2O by distillation, addition of ClSO3H, addition of base to give an alkali metal salt of 1,2-benzisoxazole-3-methanesulfonic acid, addition of POCl3 to give 1,2-benzisoxazole-3-methanesulfonyl chloride, and addition of NH3.

IT **68291-97-4P**, 1,2-Benzisoxazole-3-methanesulfonamide
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of benzisoxazolemethanesulfonamide from hydroxycoumarin)

RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)

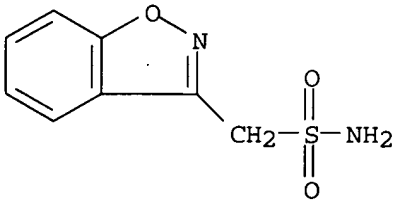


L10 ANSWER 5 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1015842 HCAPLUS
DOCUMENT NUMBER: 144:141916
TITLE: Stability of Salivary Concentrations of the Newer Antiepileptic Drugs in the Postal System
AUTHOR(S): Jones, Mikael D.; Ryan, Melody; Miles, Michael V.; Tang, Peter H.; Fakhoury, Toufic A.; De Grauw, Ton J.; Baumann, Robert J.
CORPORATE SOURCE: University of Kentucky Chandler Medical Center, Lexington, KY, 40536-0082, USA
SOURCE: Therapeutic Drug Monitoring (2005), 27(5), 576-579
CODEN: TDMODV; ISSN: 0163-4356
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Saliva antiepileptic drug (AED) concns. strongly correlate with serum concns. Saliva collection is painless and noninvasive, and untrained personnel can easily be taught the collection **process.** Remote patients could mail saliva samples to a laboratory for monitoring, and samples could be obtained in the immediate postictal state to provide a "real-time" concentration The objectives of this study were to assess the stability of saliva lamotrigine (LMT), levetiracetam (LEV), oxcarbazepine (OXC), topiramate (TPM), and zonisamide (ZNS) concns. sent through the United States Postal Service (USPS) and to quantify the amount of time needed for patients and the USPS to return samples to clinic. Saliva samples were obtained from patients currently taking 1 of the targeted AEDs. Samples were split into 2 storage vials. One sample was sealed in an addressed envelope, which the patient mailed from home, whereas the other sample was frozen immediately. Postmark date and day returned were collected for mailed samples. Saliva concns. were determined using HPLC. Wilcoxon rank sum tests were used to compare the immediately-frozen and mailed sample means. Correlations were determined by the Spearman test. Thirty-seven patients were enrolled in the study. The median time between collection and postmark was 1 day (range 0-6 days); and between collection and receipt was 4 days (range 1-160 days). The mean concns. for mailed and immediately frozen samples were similar for each AED ($P > 0.15$). Spearman rank order correlations between mailed and immediately frozen aliquots were strong (LMT rs = 1, LEV rs = 1, OXC rs = 0.964, TPM rs = 0.90, and ZNS rs = 1). Saliva samples mailed by patients maintain stability and can be returned in a reasonable length of time. Further studies are needed to assess patient/caretaker capability of obtaining an adequate sample.

IT **68291-97-4**, Zonisamide
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saliva sample of antiepileptic drug zonsiamide mailed via United States postal service by patient maintained stability with no significant difference in drug concentration and can be returned in reasonable length of time)

RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:611671 HCAPLUS
DOCUMENT NUMBER: 143:126805
TITLE: Method of biochemical treatment of persistent pain by inhibiting biochemical mediators of inflammation
INVENTOR(S): Omoigui, Osemwota Sota
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 40 pp., Cont.-in-part of U.S.

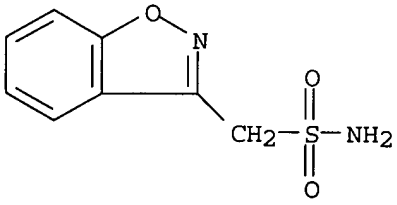
Ser. No. 224,743.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005152905	A1	20050714	US 2005-58371	20050216
US 2004038874	A1	20040226	US 2002-224743	20020822
PRIORITY APPLN. INFO.:			US 2002-224743	A2 20020822

AB The invention discloses a method for the biochem. treatment of persistent pain disorders by inhibiting the biochem. mediators of inflammation in a subject, comprising administering to the subject any one of several combinations of components that are inhibitors of biochem. mediators of inflammation. The **process** for biochem. treatment of persistent pain disorders is based on Sota Omoigui's Law, which states: 'The origin of all pain is inflammation and the inflammatory response'. Sota Omoigui's Law of Pain unifies all pain syndromes as sharing a common origin of inflammation and the inflammatory response. The various biochem. mediators of inflammation are present in differing amts. in all pain syndromes and are responsible for the pain experience. Classification and treatment of pain syndromes should depend on the complex inflammatory profile. A variety of mediators are generated by tissue injury and inflammation. These include substances produced by damaged tissue, substances of vascular origin as well as substances released by nerve fibers themselves, sympathetic fibers and various immune cells. Biochem. mediators of inflammation that are targeted for inhibition include but are not limited to: prostaglandin, nitric oxide, tumor necrosis factor α, interleukin 1α, interleukin 1β, interleukin 4, Interleukin 6, and interleukin 8, histamine and serotonin, substance P, matrix metalloproteinase, calcitonin gene-related peptide, vasoactive intestinal peptide, as well as the potent inflammatory mediator peptide proteins neurokinin A, bradykinin, kallidin and T-kinin.

IT **68291-97-4**, Zonisamide
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biochem. treatment of persistent pain by inhibiting biochem. mediators of inflammation)

RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



L10 ANSWER 7 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:485667 HCAPLUS
DOCUMENT NUMBER: 143:165983
TITLE: Ligand-Based Virtual Screening and in Silico Design of New Antimalarial Compounds Using Nonstochastic and

Stochastic Total and Atom-Type Quadratic Maps

AUTHOR(S): Marrero-Ponce, Yovani; Iyarreta-Veitia, Maite; Montero-Torres, Alina; Romero-Zaldivar, Carlos; Brandt, Carlos A.; Avila, Priscilla E.; Kirchgatter, Karin; Machado, Yanetsy

CORPORATE SOURCE: Department of Pharmacy, Faculty of Chemical Pharmacy and Department of Drug Design, Chemical Bioactive Center, Central University of Las Villas, Santa Clara, Villa Clara, 54830, Cuba

SOURCE: Journal of Chemical Information and Modeling (2005), 45(4), 1082-1100
CODEN: JCISD8; ISSN: 1549-9596

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

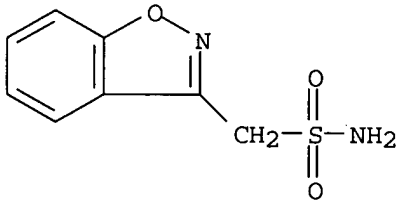
OTHER SOURCE(S): CASREACT 143:165983

AB Malaria has been one of the most significant public health problems for centuries. It affects many tropical and subtropical regions of the world. The increasing resistance of Plasmodium spp. to existing therapies has heightened alarms about malaria in the international health community. Nowadays, there is a pressing need for identifying and developing new drug-based antimalarial therapies. In an effort to overcome this problem, the main purpose of this study is to develop simple linear discriminant-based quant. structure-activity relation (QSAR) models for the classification and prediction of antimalarial activity using some of the TOMOCOMD-CARDD (TOpol. Mol. COMputer Design-Computer Aided "Rational" Drug Design) fingerprints, to enable computational screening from virtual combinatorial datasets. In this sense, a database of 1562 organic chems. having great structural variability, 597 of them antimalarial agents and 965 compds. having other clin. uses, was analyzed and presented as a helpful tool, not only for theor. chemists but also for other researchers in this area. This series of compds. was processed by a k-means cluster anal. to design training and predicting sets. Afterward, two linear classification functions were derived to discriminate between antimalarial and nonantimalarial compds. The models (including nonstochastic and stochastic indexes) correctly classify more than 93% of the compound set, in both training and external prediction datasets. They showed high Matthews' correlation coeffs., 0.889 and 0.866 for the training set and 0.855 and 0.857 for the test one. The models' predictivity was also assessed and validated by the random removal of 10% of the compds. to form a new test set, for which predictions were made using the models. The overall means of the correct classification for this **process** (leave group 10% full-out cross validation) using the equations with nonstochastic and stochastic atom-based quadratic fingerprints were 93.93% and 92.77%, resp. The quadratic maps-based TOMOCOMD-CARDD approach implemented in this work was successfully compared with four of the most useful models for antimalarials selection reported to date. The developed models were then used in a simulation of a virtual search for Ras FTase (FTase = farnesyltransferase) inhibitors with antimalarial activity; 70% and 100% of the 10 inhibitors used in this virtual search were correctly classified, showing the ability of the models to identify new lead antimalarials. Finally, these two QSAR models were used in the identification of previously unknown antimalarials. In this sense, three synthetic intermediaries of quinolinic compds. were evaluated as active/inactive ones using the developed models. The synthesis and biol. evaluation of these chems. against two malaria strains, using chloroquine as a reference, was performed. An accuracy of 100% with the theor. predictions was observed Compound 3 showed antimalarial activity, being the first report of an arylaminomethylenemalonate having such behavior. This result opens

a door to a virtual study considering a higher variability of the structural core already evaluated, as well as of other chems. not included in this study. We conclude that the approach described here seems to be a promising QSAR tool for the mol. discovery of novel classes of antimalarial drugs, which may meet the dual challenges posed by drug-resistant parasites and the rapid progression of malaria illnesses.

IT **68291-97-4**, Zonisamide
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ligand-based virtual screening and design of antimalarial compds.)

RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 111 THERE ARE 111 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:429406 HCAPLUS
DOCUMENT NUMBER: 142:482033
TITLE: A **process** for the manufacture of zonisamide, useful as anticonvulsant agent
INVENTOR(S): Jaweed Mukarram, Siddiqui Mohammed; Merwade, Aravind Yehanathsa; Shukla, Jagdish Dattopant; Saiyad, Anis Mushtaqeali
PATENT ASSIGNEE(S): Wockhardt Limited, India
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005044808	A1	20050519	WO 2003-IB5052	20031111
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003276531	A1	20050526	AU 2003-276531	20031111
PRIORITY APPLN. INFO.:			WO 2003-IB5052 A	20031111
OTHER SOURCE(S):		CASREACT 142:482033		

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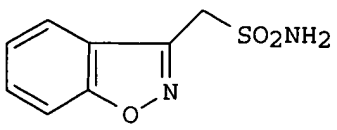


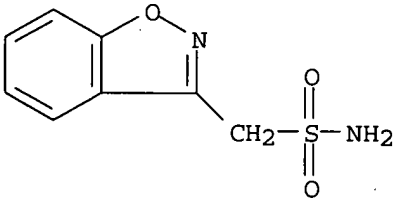
I

AB The invention relates to an improved **process** for the preparation of zonisamide (I), a well known anticonvulsant. Other aspects of this invention are isolation of a key intermediate, viz., isolation of crystalline sodium chloride associated with 1,2-benzisoxazole-3-methane sodium sulfonate (BOS-Na:NaCl). Zonisamide (I, 99% HPLC purity) was prepared via ring opening/cyclization of 4-hydroxycoumarin in the presence of NH2OH (step 1), sulfonation of the obtained 1,2-benzisoxazole-3-acetic acid, and chlorination/amidation of the obtained sodium 1,2-benzisoxazole-3-methanesulfonate associated with NaCl (yield of step 1 was 95-98%). The anal. characteristics like IR and XRD data of BOS-Na:NaCl were also reported to confirm its nature.

IT **68291-97-4P**, Zonisamide
RL: IMF (Industrial manufacture); PRP (Properties); PREP (Preparation)
(**process** for the manufacture of zonisamide useful as anticonvulsant agent)

RN 68291-97-4 HCAPLUS

CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:369133 HCAPLUS

DOCUMENT NUMBER: 142:435774

TITLE: Compositions treatment of chronic inflammatory diseases

INVENTOR(S): Shapiro, Howard K.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 44 pp., Cont.-in-part of U.S. Ser. No. 610,073, abandoned.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005090553	A1	20050428	US 2004-924945	20040824

PRIORITY APPLN. INFO.: US 1992-906909 B2 19920630
US 1994-241603 B2 19940511
US 1997-814291 B2 19970310
US 2000-610073 B2 20000705

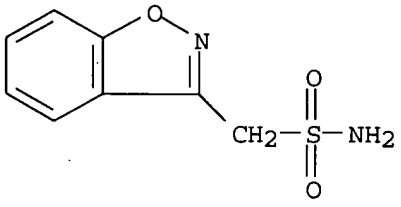
OTHER SOURCE(S): MARPAT 142:435774

AB This invention defines novel compns. that can be used for clin. treatment of a class of chronic inflammatory diseases. Increased generation of carbonyl substances, aldehydes and ketones, occurs at sites of chronic inflammation and is common to the etiologies of all of the clin. disorders addressed herein. Such carbonyl substances are cytotoxic and addnl. serve to perpetuate and disseminate the inflammatory **process.** This invention defines use of compns., the orally administered required primary agents of which are primary amine derivs. of benzoic acid capable of reacting with the carbonyl substances. P-Aminobenzoic acid (or PABA) is an example of the required primary agent of the present invention. PABA has a small mol. weight, is water soluble, has a primary amine group which reacts with carbonyl-containing substances and is tolerated by the body in relatively high dosages for extended periods. The method of the present invention includes administration of a composition comprising: (1) an orally consumed primary agent; (2) a previously known medicament co-agent recognized as effective to treat a chronic inflammatory disease addressed herein administered to the mammalian subject via the oral route, other systemic routes of administration or via the topical route; and (3) optionally 1 or more addnl. orally consumed co-agent selected from the group consisting of antioxidants, vitamins, metabolites at risk of depletion, sulfhydryl co-agents, co-agents which may facilitate glutathione activity and nonabsorbable primary amine polymeric co-agents, so as to produce an additive or synergistic physiol. effect of an anti-inflammatory nature.

IT **68291-97-4**, Zonisamide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. treatment of chronic inflammatory diseases)

RN 68291-97-4 HCAPLUS

CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



L10 ANSWER 10 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:300420 HCAPLUS

DOCUMENT NUMBER: 142:373849

TITLE: An improved **process** for preparation of isoxazole and oxathiane derivatives, useful as intermediates for synthesis of zonisamide

INVENTOR(S): Veera Reddy, Arya; Rajendiran, Chinnapillai; Vaishali, Nadkarni; Jasti, Venkat

PATENT ASSIGNEE(S): Suven Life Sciences Limited, India

SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005030738	A1	20050407	WO 2003-IN325	20030929
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003304484	A1	20050414	AU 2003-304484	20030929
PRIORITY APPLN. INFO.:			WO 2003-IN325 A	20030929
OTHER SOURCE(S):		CASREACT 142:373849; MARPAT 142:373849		

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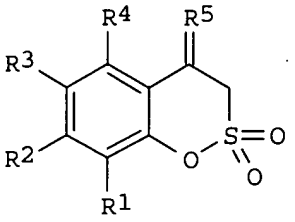

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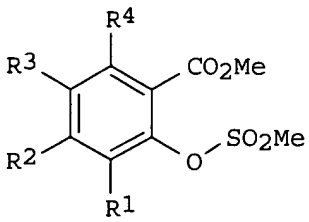
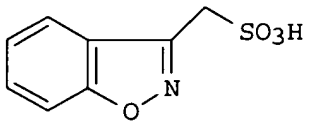


II

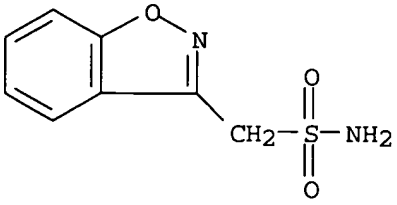


IV

AB The invention relates to an improved **process** for preparation of benzisoxazole and oxathiane derivs., e.g. I [wherein: R1, R2, R3, and R4 are independently selected from H, alkyl, chloro, bromo, NO2, or NMe2, etc.; R5 is N(OH)], useful for the preparation of zonisamide. The compds. of the formula I were prepared by intramol. cyclocondensation of the compound of the formula II and subsequent imination of the obtained ketone I (R5 = O) by NH2OH. For instance, III [I, R1 = R2 = R3 = R4 = H, R5 = N(OH)] was prepared via cyclocondensation of II (R1 = R2 = R3 = R4 = H) and subsequent imination of I (R1 = R2 = R3 = R4 = H, R5 = O) by NH2OH•HCl (yields: cyclization - 76%, imination - 93%). Benzisoxazole derivative IV•Na was prepared via ring-opening/cyclization of III with a purity of 93.26%.

IT **68291-97-4P**, 1,2-Benzisoxazole-3-methanesulfonamide
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(improved **process** for preparation of isoxazole and oxathiane

derivs. useful for the preparation of zonisamide)
RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

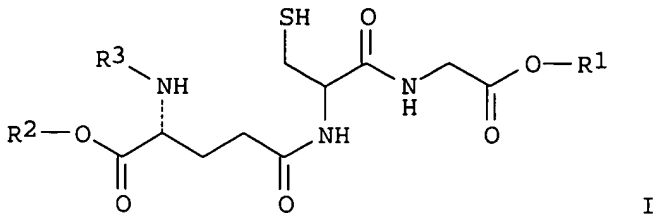
L10 ANSWER 11 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:1060673 HCAPLUS
DOCUMENT NUMBER: 142:32914
TITLE: Sensitive and selective in vitro assay for the detection of reactive drug intermediates
INVENTOR(S): Cole, Mark J.; Harriman, Shawn P.; Soglia, John R.
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 30 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004248234	A1	20041209	US 2004-863164	20040608
WO 2004109279	A2	20041216	WO 2004-IB1497	20040601
WO 2004109279	A3	20050127		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-477472P P 20030609
US 2004-546443P P 20040219

GI



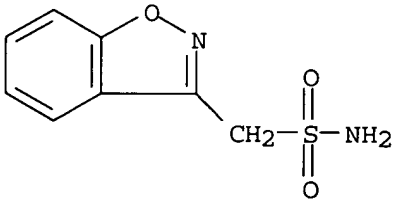
I

AB In vitro **processes** for detecting one or more reactive metabolites that may be formed from a substrate (e.g., a drug or a potential drug candidate) by an enzyme system is disclosed. The substrate is contacted in a mixture with an enzyme system (e.g., with a microsomal drug metabolizing enzyme system, such as a P 450 system) to form reactive species (e.g., reactive metabolites), which in the same or a different mixture are contacted with a glutathione compound with formula I (where R1 = Me, Et, etc., R2 = Me, Et, etc., R3 = (benzyloxy)carbonyl, (arylalkoxy)carbonyl, etc.; e.g., glutathione Et ester) that reacts with the reactive species to form detectable species (e.g., glutathione Et ester conjugates). Preferably, solid phase extraction, high performance liquid chromatog., electrospray ionization, and tandem triple quadropole mass spectrometry are used for detection. The **processes** may be used in the early stages of a drug discovery program, as well as in other contexts.

IT **68291-97-4**, Zonisamide
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sensitive and selective in vitro assay for detection of reactive drug intermediates)

RN 68291-97-4 HCAPLUS

CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



L10 ANSWER 12 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:716302 HCAPLUS

DOCUMENT NUMBER: 141:248702

TITLE: Method for preparing 1,2-dichloroethane-free zonisamide crystals

INVENTOR(S): Ueno, Ryoichi; Kimura, Yasujiro

PATENT ASSIGNEE(S): Dainippon Pharmaceutical Co., Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

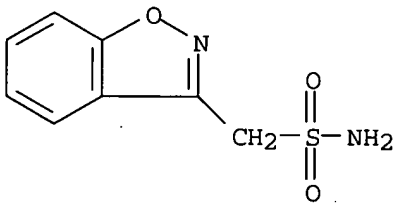
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2004244410	A2	20040902	JP 2003-285878	20030804
PRIORITY APPLN. INFO.:			JP 2003-13587 A	20030122

AB The title method for the preparation of crystals of zonisamide containing ≤ 5 ppm residual 1,2-dichloroethane (I) comprises adding aqueous C2 - C4 alc. (e.g., isopropanol + water) to zonisamide crystals which contain > 5 ppm residual I, removing I from this mixture by azeotropic distillation, collecting the zonisamide crystals from the residual mixture Thus, zonisamide containing < 1 ppm I was obtained by the title method. Zonisamide is a known antiepileptic.

IT **68291-97-4P**, Zonisamide
RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(method for preparing 1,2-dichloroethane-free zonisamide crystals with azeotropic distillation, followed by crystallization)

RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



L10 ANSWER 13 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:606452 HCAPLUS
DOCUMENT NUMBER: 141:140420
TITLE: A **process** for the preparation of benzo[d]isoxazol-3-yl-methanesulfonic acid
INVENTOR(S): Razzetti, Gabriele; Mantegazza, Simone; Castaldi, Graziano; Allegrini, Pietro; Lucchini, Vittorio; Bologna, Alberto
PATENT ASSIGNEE(S): Dinamite Dipharma S.P.A., Italy
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004063173	A1	20040729	WO 2003-EP14919	20031224

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RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,

BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK,
TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2512791	AA	20040729	CA 2003-2512791	20031224
AU 2003298248	A1	20040810	AU 2003-298248	20031224
EP 1581508	A1	20051005	EP 2003-795972	20031224

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

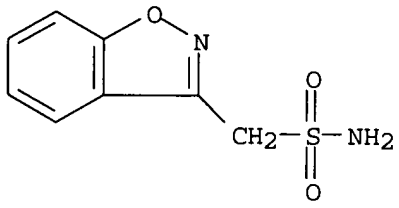
PRIORITY APPLN. INFO.:	IT 2003-MI26	A	20030110
	IT 2003-MI1383	A	20030704
	WO 2003-EP14919	W	20031224

OTHER SOURCE(S): CASREACT 141:140420

AB The title compound (I) or its salt, useful as an intermediate in the preparation of anticonvulsant zonisamide, is prepared by reaction of 1,2-benzoxathin-4(3H)-one 2,2-dioxide oxime (II) with organic base or alkali or alkaline earth hydroxide. Thus, reaction of II with aq NaOH at room temperature for 3 h gave 70% sodium salt of I.

IT **68291-97-4P**, Zonisamide
RL: PNU (Preparation, unclassified); PREP (Preparation)
(preparation of 1,2-benzisoxazole-3-methanesulfonic acid or its salt as intermediate for zonisamide)

RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



L10 ANSWER 14 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	2004:569889 HCAPLUS
DOCUMENT NUMBER:	141:106458
TITLE:	Azeotropic distillation **process** for the preparation of 1,2-dichloroethane-free crystals of zonisamide
INVENTOR(S):	Ueno, Yoshikazu; Kimura, Yasujiro
PATENT ASSIGNEE(S):	Japan
SOURCE:	U.S. Pat. Appl. Publ., 5 pp., Cont. of U.S. Ser. No. 462,595, abandoned. CODEN: USXXCO
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004138474	A1	20040715	US 2003-733566	20031212
WO 2004063174	A1	20040729	WO 2003-JP9530	20030728

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

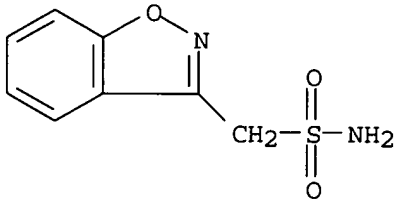
GM, HR, HU, ID, IL, IN, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT,
LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH,
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT,
TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2003249010	A1	20040810	AU 2003-249010	20030728
EP 1583748	A1	20051012	EP 2003-815138	20030728
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2005080269	A1	20050414	US 2003-636593	20030808
PRIORITY APPLN. INFO.:			US 2003-340601	B1 20030113
			US 2003-462595	B1 20030617
			WO 2003-JP9530	W 20030728

AB A **process** for the preparation of crystals of zonisamide containing residual 1,2-dichloroethane of ≤5 ppm comprises adding an aqueous C2-4 alc. (e.g., aqueous 2-propanol) to crystals of zonisamide containing residual 1,2-dichloroethane of >5 ppm, removing the 1,2-dichloroethane by azeotropic distillation, followed by collecting the precipitated crystals from the residual mixture

IT **68291-97-4P**, Zonisamide
RL: PEP (Physical, engineering or chemical process); PUR (Purification or recovery); PYP (Physical process); PREP (Preparation); PROC (Process)
(azeotropic distillation **process** for the preparation of 1,2-dichloroethane-free crystals of zonisamide)

RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



L10 ANSWER 15 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:569888 HCAPLUS
DOCUMENT NUMBER: 141:106457
TITLE: Azeotropic distillation **process** for the preparation of 1,2-dichloroethane-free crystals of zonisamide
INVENTOR(S): Ueno, Yoshikazu; Kimura, Yasujiro
PATENT ASSIGNEE(S): Dainippon Pharmaceutical Co., Ltd., Japan
SOURCE: U.S. Pat. Appl. Publ., 5 pp., Cont.-in-part of U.S. Ser. No. 462,726, abandoned.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

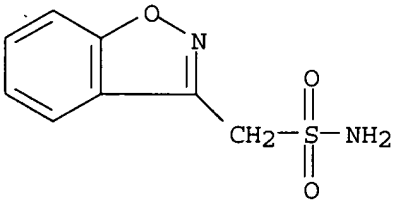
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 2004138473	A1	20040715	US 2003-733565	20031212
US 6900333	B2	20050531		
WO 2004063174	A1	20040729	WO 2003-JP9530	20030728
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003249010	A1	20040810	AU 2003-249010	20030728
EP 1583748	A1	20051012	EP 2003-815138	20030728
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2005080269	A1	20050414	US 2003-636593	20030808
PRIORITY APPLN. INFO.:			US 2003-340601	B3 20030113
			US 2003-462726	B1 20030617
			WO 2003-JP9530	W 20030728

AB A **process** for the preparation of crystals of zonisamide containing residual 1,2-dichloroethane of ≤5 ppm comprises adding an aqueous C2-4 alc. (e.g., aqueous 2-propanol) to crystals of zonisamide containing residual 1,2-dichloroethane of >5 ppm, removing the 1,2-dichloroethane by azeotropic distillation, followed by collecting the precipitated crystals from the residual mixture

IT **68291-97-4P**, Zonisamide
RL: PEP (Physical, engineering or chemical process); PUR (Purification or recovery); PYP (Physical process); PREP (Preparation); PROC (Process)
(azeotropic distillation **process** for the preparation of 1,2-dichloroethane-free crystals of zonisamide)

RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 16 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:252201 HCAPLUS
DOCUMENT NUMBER: 140:229472
TITLE: Method using dopamine activity-modulating anticonvulsants for treatment of disorders of personal attachment and deficient social interaction
INVENTOR(S): Daniel, David Gordon
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 5 pp.

CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

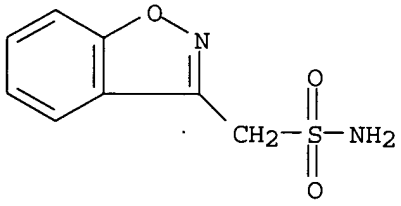
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004058997	A1	20040325	US 2002-252716	20020924

PRIORITY APPLN. INFO.: US 2002-252716 20020924

AB The invention provides a **process** for treatment of central nervous system disorders characterized by interpersonal discomfort and awkwardness, diminished social approach and initiative, and paucity of interpersonal attachments and social interactions. Abnormal perceptions of interpersonal communication and peculiarities of social behavior commonly accompany these symptoms. Inhibited initiation of social behavior and personal attachment are cardinal symptoms of schizotypal personality disorder, schizoid personality disorder, paranoid personality disorder, avoidant personality disorder; pervasive developmental disorder, and Aspberger's syndrome. These symptoms may also in the form of clin. significant social introversion that does not meet the threshold for a formal psychiatric disorder by current diagnostic stds. such as DSM-IV. The treatment provides a **process** of symptomatic relief and stabilization of the course of these disorders. The methodol. of the invention uses administration of an anticonvulsant which modulates dopamine activity.

IT **68291-97-4**, Zonisamide
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dopamine activity-modulating anticonvulsants for treatment of disorders of personal attachment and deficient social interaction)

RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



L10 ANSWER 17 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:162447 HCAPLUS
DOCUMENT NUMBER: 140:193061
TITLE: Method of treatment of persistent pain by inhibiting mediators of inflammation
INVENTOR(S): Omoigui, Osemwota
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 14 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004038874	A1	20040226	US 2002-224743	20020822
US 2005152905	A1	20050714	US 2005-58371	20050216

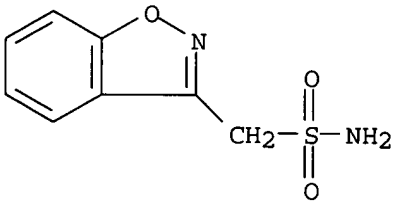
PRIORITY APPLN. INFO.: US 2002-224743 A2 20020822

AB This invention relates to a method for treating persistent pain disorders by inhibiting the biochem. mediators of inflammation in a subject comprising administering to said subject a therapeutically effective dosage of said inhibitor. Said **process** for treating persistent pain disorders is based on Sota Omoigui's Law, which states: The origin of all pain is inflammation and the inflammatory response. Biochem. mediators of inflammation that are targeted for inhibition include but are not limited to: prostaglandin, nitric oxide, tumor necrosis factor alpha, interleukin 1-alpha, interleukin 1-beta, interleukin-4, Interleukin-6 and interleukin-8, histamine and serotonin, substance P, Matrix Metallo-Proteinase, calcitonin gene-related peptide, vasoactive intestinal peptide as well as the potent inflammatory mediator peptide proteins neurokinin A, bradykinin, kallidin and T-kinin.

IT **68291-97-4**, Zonisamide
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as nitric oxide inhibitor; persistent pain treatment by inhibiting mediators of inflammation)

RN 68291-97-4 HCAPLUS

CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



L10 ANSWER 18 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:696874 HCAPLUS

DOCUMENT NUMBER: 139:230763

TITLE: Method for preparing 1,2-benzisoxazole-3-methanesulfonyl chloride using thionyl chloride, and its amidation to form zonisamide

INVENTOR(S): Mendelovici, Marioara; Gershon, Neomi; Nidam, Tamar; Pilarski, Gideon; Sterinbaum, Greta

PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.

SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003072552	A1	20030904	WO 2003-US5690	20030224
WO 2003072552	C1	20040923		

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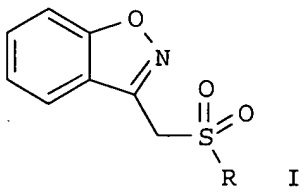
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2475598	AA	20030904	CA 2003-2475598		20030224
AU 2003219889	A1	20030909	AU 2003-219889		20030224
US 2004014983	A1	20040122	US 2003-373554		20030224
US 6936720	B2	20050830			
EP 1472236	A1	20041103	EP 2003-716172		20030224
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
CN 1636002	A	20050706	CN 2003-804328		20030224
JP 2005526049	T2	20050902	JP 2003-571258		20030224
NO 2004003972	A	20040922	NO 2004-3972		20040922
PRIORITY APPLN. INFO.:			US 2002-358916P	P	20020222
			WO 2003-US5690	W	20030224

OTHER SOURCE(S): CASREACT 139:230763; MARPAT 139:230763
GI



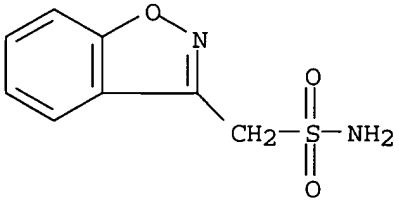
I

AB The invention relates to a **process** of preparing 1,2-benzisoxazole-3-methanesulfonic acid chloride (I; R = Cl) (II). This compound is useful as an intermediate for preparation of the antiepileptic agent zonisamide (I; R = NH2) (III). II is prepared via chlorination of the acid I (R = OH), or its salts or esters, using thionyl chloride (SOCl2). III is prepared by amidation of II using NH3 in either aqueous, anhydrous, or masked forms. More specifically, the invention provides a **process** of preparing III, comprising the steps of : (1) chlorinating I (R = OH) or its salts or esters with SOCl2 in an organic solvent and/or in the presence of a catalyst to form II; and (2) amidating II in the presence of ammonia, the latter selected from the group consisting of (i) aqueous ammonia in a biphasic system, (ii) masked ammonia, and (iii) dry ammonia, to form III. Use of SOCl2 to form the acid chloride avoids the use of POCl3, which is substantially more hazardous in the workplace. For instance, 4 equiv SOCl2 was added dropwise over 3 h to a mixture of 1 equiv I (R = OH) Na salt in PhMe containing 0.1 equiv DMF catalyst at 50-60°, followed by stirring at 50° for 4-5 h. Excess SOCl2 was removed by flowing N2, fresh PhMe was added, and inorg. salts were filtered to give a solution of II in PhMe. This solution was cooled to 10-15° and anhydrous NH3(g) was bubbled through the mixture at that temperature until the reaction was complete.

by HPLC. Filtration of inorg. salts, trituration with H2O at room temperature, filtration, and washing with 95% EtOH gave crude III in 91.25% yield, containing only 2.5% I.NH3 (R = OH) (IV) as an impurity. Recrystn. from refluxing 95% with active C treatment, filtration, and slow cooling, gave III in 90.8% yield with only 0.02% IV.

IT **68291-97-4P**, Zonisamide
RL: IMF (Industrial manufacture); PUR (Purification or recovery); SPN (Synthetic preparation); PREP (Preparation)
(product; preparation of benzisoxazolemethanesulfonyl chloride using thionyl chloride, and its amidation to form zonisamide)

RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 19 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:590879 HCAPLUS
DOCUMENT NUMBER: 139:154994
TITLE: Novel sulfonation method for zonisamide intermediate in zonisamide synthesis and their novel crystal forms
INVENTOR(S): Nidam, Tamar; Mendelovici, Marioara; Schwartz, Edward; Wizel, Shlomit
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel
SOURCE: U.S. Pat. Appl. Publ., 35 pp., Cont.-in-part of U.S. Ser. No. 233,190.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003144527	A1	20030731	US 2002-288135	20021105
US 7015330	B2	20060321		
US 2003114682	A1	20030619	US 2002-233190	20020829
US 6841683	B2	20050111		
WO 2004020419	A1	20040311	WO 2002-US35537	20021105

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

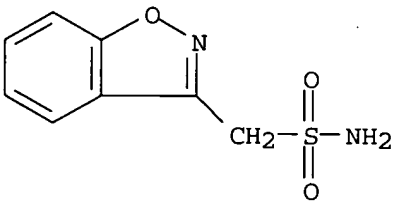
AU 2002354044	A1	20040319	AU 2002-354044		20021105
US 2004138471	A1	20040715	US 2003-662966		20030915
US 2004138472	A1	20040715	US 2003-662986		20030915
US 2005027126	A1	20050203	US 2004-928313		20040830
US 2006063936	A1	20060323	US 2005-271755		20051114
US 2006069267	A1	20060330	US 2005-271839		20051114
PRIORITY APPLN. INFO.:			US 2001-316109P	P	20010830
			US 2001-344439P	P	20011024
			US 2002-233190	A2	20020829
			US 2002-288135	A3	20021105
			WO 2002-US35537	W	20021105

AB The present invention relates to a novel sulfonation of an intermediate of zonisamide. The sulfonation **processes** using chlorosulfonic acid as well as acetic anhydride and sulfuric acid in an organic solvent are disclosed. Crystalline forms of benzisoxazole methanesulfonic acid (BOS-H) and its salts (BOS-Na, BOS-Ca, and BOS-Ba) and their novel preparation **processes** are disclosed.

IT **68291-97-4P**, Zonisamide
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(benzisoxazole acetic acid sulfonation and intermediates crystal forms in zonisamide synthesis)

RN 68291-97-4 HCAPLUS

CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 20 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:202630 HCAPLUS

DOCUMENT NUMBER: 138:221579

TITLE: **Process** for the preparation of 1,2-benzisoxazole-3-methanesulfonic acid and its salts, intermediates in the synthesis of Zonisamide

INVENTOR(S): Nidam, Tamar; Mendelovici, Marioara; Schwartz, Eduard; Wizel, Shlomit

PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.

SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003020708	A1	20030313	WO 2002-US27593	20020829
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2458905	AA	20030313	CA 2002-2458905	20020829
EP 1430037	A1	20040623	EP 2002-768748	20020829
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2005506980	T2	20050310	JP 2003-524979	20020829
PRIORITY APPLN. INFO.:			US 2001-316109P	P 20010830
			US 2001-344439P	P 20011024
			WO 2002-US27593	W 20020829

OTHER SOURCE(S): CASREACT 138:221579
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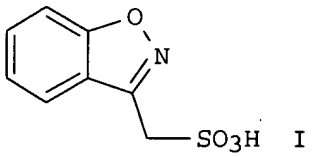
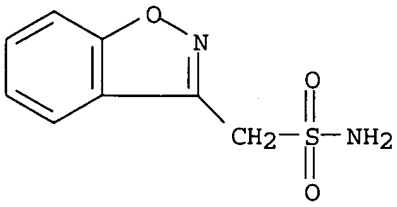


I

AB A **process** for the preparation of 1,2-benzisoxazole-3-methanesulfonic acid (I) by sulfonation of 1,2-benzisoxazole-3-acetic acid with chlorosulfonic acid or acyl sulfates in an organic solvent and optional conversion to its salts is disclosed. I has com. importance as a key intermediate in the preparation of Zonisamide. For example, a solution of 1,2-benzisoxazole-3-acetic acid (20 gm), 98% H2SO4 (22 gm), and Ac2O (23 gm) in AcOEt (80 mL) was heated at reflux for 4 h and the cooled reaction mixture treated with aqueous 10% aqueous NaOH (120 mL) to give I•Na (20.33 gm) in 100% purity. Advantages of the present invention are: (1) the preparation of I without the use of dioxane, improving the environmental safety of the reaction; and (2) the increased selectivity for preparation of the monosulfonated over the bisulfonated benzisoxazole. Crystalline forms of 1,2-benzisoxazole-3-methanesulfonic acid (BOS-H) and its salts (BOS-Na, BOS-Ca, and BOS-Ba) were also characterized.

IT **68291-97-4P**, Zonisamide
RL: IMF (Industrial manufacture); PREP (Preparation)
(target product; preparation of benzisoxazolemethanesulfonic acid and salts, intermediates in the synthesis of Zonisamide, by sulfonation of benzisoxazoleacetic acid)

RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)

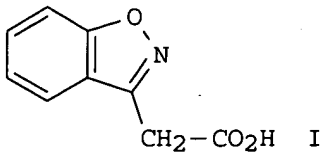


REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 21 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:695963 HCAPLUS
DOCUMENT NUMBER: 137:216942
TITLE: **Process** for the preparation of 1,2-benzisoxazole-3-acetic acid, an intermediate in the synthesis of zonisamide
INVENTOR(S): Mendelovici, Mariorara; Nidam, Tamar
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002070495	A1	20020912	WO 2002-US6419	20020304
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2440030	AA	20020912	CA 2002-2440030	20020304
US 2002183525	A1	20021205	US 2002-90710	20020304
US 6677458	B2	20040113		
EP 1373229	A1	20040102	EP 2002-717527	20020304
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004049053	A1	20040311	US 2003-661109	20030912
PRIORITY APPLN. INFO.:			US 2001-273172P	P 20010302
			US 2001-294847P	P 20010531
			US 2002-90710	A3 20020304
			WO 2002-US6419	W 20020304

OTHER SOURCE(S): CASREACT 137:216942
GI



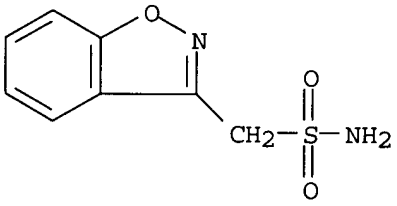
I

AB A **process** for the preparation of 1,2-benzisoxazole-3-acetic acid (I) from 4-hydroxycoumarin and hydroxylamine.HCl in the presence of a base is disclosed. Compound I has com. importance as a key intermediate in the preparation of Zonisamide. For example, a solution of 4-hydroxycoumarin (100 g), hydroxylamine hydrochloride (150 g) and diethylamine (160 g) in MeOH (500 mL) was heated at reflux for 1 h. The reaction mixture was evaporated to dryness and the solid dissolved in aqueous NaHCO3 and extracted with ether. After acidification of the aqueous phase, the product was isolated by filtration, washed with water and dried to provide I (99.82 g) in 93 % weight/weight yield. Avantages of the present invention are: (1) the prepare of I without the use of metallic sodium; and (2) the minimization of reaction side-products, e.g., oxime. The **process** is thus substantially less hazardous than previous methods. The invention also claims the prepare I or salts of which are converted to 1,2-benzisoxazole-3-methanesulfonamide, i.e., zonisamide.

IT **68291-97-4P**, 1,2-Benzisoxazole-3-methanesulfonamide
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(product; **process** for preparation of 1,2-benzisoxazole-3-acetic acid, an intermediate in synthesis of zonisamide)

RN 68291-97-4 HCAPLUS

CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 22 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:912503 HCAPLUS

DOCUMENT NUMBER: 136:177486

TITLE: Carbonic Anhydrase Inhibitors: Anticonvulsant Sulfonamides Incorporating Valproyl and Other Lipophilic Moieties

AUTHOR(S): Masereel, Bernard; Rolin, Stephanie; Abbate, Francesco; Scozzafava, Andrea; Supuran, Claudiu T.

CORPORATE SOURCE: Department of Pharmacy, University of Namur, FUNDP, Namur, B-5000, Belg.

SOURCE: Journal of Medicinal Chemistry (2002), 45(2), 312-320
CODEN: JMCMAR; ISSN: 0022-2623

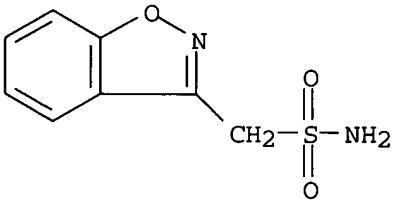
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:177486

AB A series of aromatic/heterocyclic sulfonamides incorporating valproyl moieties were prepared to design antiepileptic compds. possessing in their structure two moieties known to induce such a pharmacol. activity: valproic acid, one of the most widely used antiepileptic drugs, and the sulfonamide residue included in acetazolamide and topiramate, two carbonic anhydrase inhibitors with antiepileptic properties. Some of these derivs. showed very high inhibitory potency against three carbonic anhydrase (CA) isoenzymes, such as CA I, CA II, and CA IV, involved in important physiol. **processes.** Topiramate, a recently developed antiepileptic drug possessing a sulfamate moiety, also shares this property, although earlier literature data reported this compound to be a weak-moderate CA I, II, and IV inhibitor. The valproyl derivative of acetazolamide (5-valproylamido-1,3,4-thiadiazole-2-sulfonamide) was one of the best hCA I and hCA II inhibitor in the series and exhibited very strong anticonvulsant properties in an MES test in mice. In consequence, other 1,3,4-thiadiazolesulfonamide derivs. possessing potent CA inhibitory properties and substituted with different alkyl/arylcarboxamido/sulfonamido/ureido moieties in the 5 position have been investigated for their anticonvulsant effects in the same animal model. It was observed that some lipophilic derivs., such as 5-benzoylamido-, 5-toluenesulfonylamido-, 5-adamantylcarboxamido-, and 5-pivaloylamido-1,3,4-thiadiazole-2-sulfonamide, show promising in vivo anticonvulsant properties and that these compds. may be considered as interesting leads for developing anticonvulsant or selective cerebrovasodilator drugs.

IT **68291-97-4**, Zonisamide
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sulfonamides incorporating valproyl and other lipophilic moieties as carbonic anhydrase inhibitors with anticonvulsant activity in relation to structure and lipophilicity)

RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

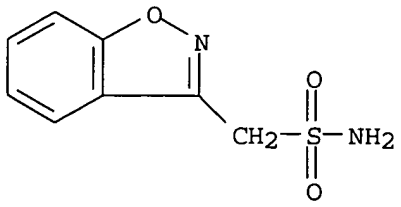
L10 ANSWER 23 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:75746 HCAPLUS
DOCUMENT NUMBER: 126:180780
TITLE: Pharmacokinetic study of zonisamide in patients undergoing brain surgery
AUTHOR(S): Ieiri, Ichiro; Morioka, Takato; Kim, Sonyori; Nishio, Shunji; Fukui, Masashi; Higuchi, Shun
CORPORATE SOURCE: Division of Pharmaceutical Science, Kyushu University, Fukuoka, Japan
SOURCE: Journal of Pharmacy and Pharmacology (1996), 48(12),

1270-1275
CODEN: JPPMAB; ISSN: 0022-3573
PUBLISHER: Royal Pharmaceutical Society of Great Britain
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To test whether the concentration of the anticonvulsant zonisamide in erythrocytes reflects the brain concentration and the clin. response of the drug, its pharmacokinetics were studied in nine patients undergoing surgery for brain tumor. Erythrocyte, total, and free serum concns. in samples drawn on the day of brain surgery were compared with levels on a day after the operation. In three patients zonisamide and its major metabolite, 2-sulfamoylacetylphenol, were also analyzed in urine. The area under the curve of the free and the erythrocyte concentration did not differ between the two study phases whereas the area under the curve of the total serum concentration was significantly lower on the day of the operation, and this was associated with significant increases in total clearance (15.4 compared with 12.7 mL kg-1 h-1, $P < 0.05$, $n = 9$) and renal clearance (5.4 compared with 3.3 mL kg-1 h-1, $P < 0.05$, $n = 3$), and non-significant change in non-renal clearance (7.7 on the day of operation compared with 8.4 mL kg-1 h-1 on the post-operation day, $n = 3$). Zonisamide distribution was also altered by the operative procedure, as evidenced by a higher volume of distribution (1.48 compared with 0.87 L kg-1, $P < 0.05$, $n = 9$). The binding of zonisamide was characterized on both days. Zonisamide binding to erythrocytes seemed to occur by two **processes**: a saturable **process** and a non-saturable linear **process.** The maximum binding capacity to erythrocytes (31.6 vs. 29.7 μg mL-1) did not differ on the two days; however, increases in the dissociation binding constant (+28%) and the proportionality constant (+24%) were observed on the day of the operation, suggesting that the zonisamide concentration in erythrocytes was greater on the day of the operation. Brain surgery appears to be one of the possible factors altering the rate of elimination of zonisamide and the uptake of the drug by erythrocytes.

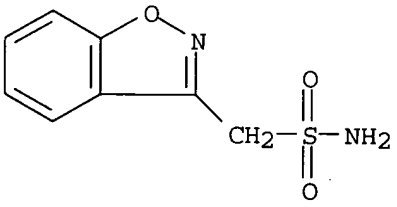
IT **68291-97-4**, Zonisamide
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(pharmacokinetic study of zonisamide in humans undergoing brain surgery)

RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



L10 ANSWER 24 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:215 HCAPLUS
DOCUMENT NUMBER: 112:215
TITLE: Binding of sulfonamides to erythrocyte proteins and possible drug-drug interaction
AUTHOR(S): Matsumoto, Katashi; Miyazaki, Hisashi; Fujii, Toshihiko; Amejima, Hideki; Furukawa, Hideo;

Hashimoto, Masahisa
CORPORATE SOURCE: Res. Lab., Dainippon Pharm. Co., Ltd., Suita, 564, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (1989), 37(10), 2807-10
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mode of binding of sulfonamides to erythrocyte proteins and possible drug-drug interaction between those compds. in erythrocytes resulting in changes in tissue levels were studied in rats using zonisamide (a novel antiepileptic agent possessing a sulfonamide group), several other sulfonamides, and some antiepileptics without a sulfonamide group. In Michaelis-Menten plottings, the sulfonamide was concentrated into erythrocytes in vitro and in vivo in a saturable high-affinity mode and in a linear low-affinity mode at ordinary therapeutic plasma levels through a simple diffusion **process.** Concentration in erythrocytes was affected by the presence of albumin in the extracellular medium. The cellular sulfonamide was readily replaced by extracellular sulfonamide in vitro. Even in vivo, erythrocyte levels of zonisamide were lowered by administration of other sulfonamides, although the plasma and tissue levels were not changed since the plasma and tissue compartments of zonisamide were large relative to the erythrocyte compartment at ordinary therapeutic dose levels of zonisamide in animals and man. Therefore, disposition of zonisamide was not influenced by other sulfonamides, but drug-drug interactions affecting the tissue levels may occur for a combination of sulfonamides with extremely different affinities for erythrocytes and low therapeutic plasma levels.
IT **68291-97-4**, Zonisamide
RL: BIOL (Biological study)
(binding of, by erythrocyte, other sulfonamides effect on)
RN 68291-97-4 HCAPLUS
CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	193.88	529.29
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-24.00	-24.00

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